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# Pioneering Work in Vertebrate Neural Development

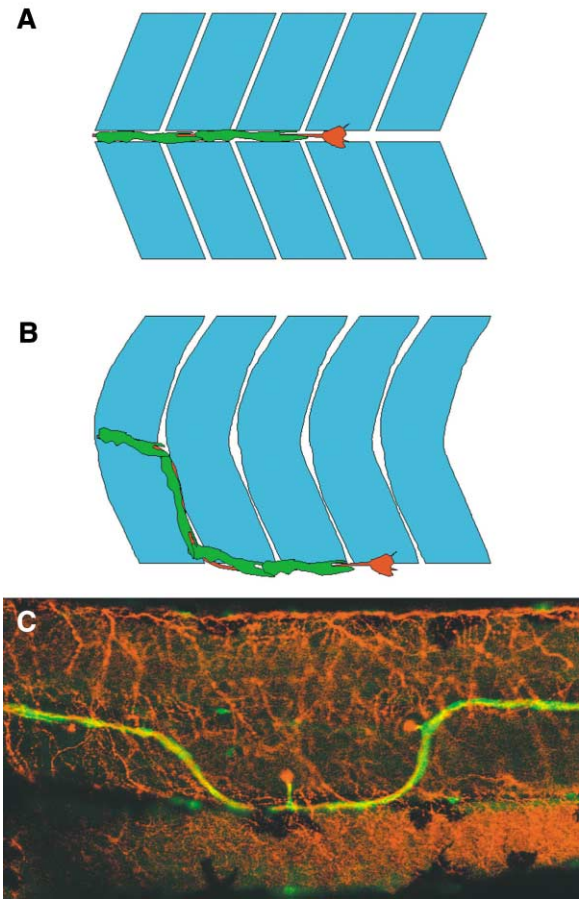
**Control of directional axon growth is fundamental to correct wiring in the nervous system, and glia are thought to play an important role. New work in the zebrafish lateral line shows that glia are not required for axonal pathfinding but are required for normal mature nerve organization.**

To understand how connections are made within the nervous system, it is essential to know how axonal growth cones are directed to appropriate target sites. Glia are thought to play a pivotal role in directing axonal growth, for example as "guideposts" along a pathway. Studies in *Drosophila* have contributed considerably to our understanding of the role of neuron-glial interactions (reviewed in Auld, 1999). For instance, ablation and mutational analysis of glia in the developing embryonic nervous system show that normally directed axon growth is dependent on the glia (Hidalgo and Booth, 2000; Hidalgo et al., 1995). Moreover, glia also play an important role in the formation and/or maintenance of axon fascicles, essential to the function of the mature nerve (Hidalgo et al., 1995; Leiserson et al., 2000). Glial migration in the *Drosophila* wing, in contrast to the embryonic nervous system, is directed by the axons (Giangrande, 1994).

Our understanding of the role of glia in vertebrate axonal guidance has not quite reached the level seen for insects, but it soon will. New results from Darren Gilmour, Hans-Martin Maischein, and Christiane Nüsslein-Volhard, published in the May 16 issue of *Neuron*, mark a new degree of sophistication in the study of vertebrate nervous system development (Gilmour et al., 2002). These investigators present a spectacular live embryo analysis of the peripheral glia and investigate their role in zebrafish lateral line nerve development. To label living glia in whole embryos, they use transgenic embryos expressing green fluorescent protein (GFP) under the control of a neural crest cell specific *zFoxD3* promoter. Using mutants that either remove the glia or misroute the forming lateral line nerve, the authors test the interdependence of lateral line axons and glia for correct migration.

The lateral line is an important sensory system for zebrafish (Gompel et al., 2001). Lateral line organs are mechanosensory structures that employ hair cells related to those of the inner ear. Lateral line organs develop around the head and at periodic intervals along the length of the embryo. Normally, a lateral line primordium migrates along the length of the body depositing organ precursors and forming the nerve as it moves from head to tail. The track followed by growing axons is defined by the dorsal-ventral boundary of somites, called the horizontal myoseptum. Neural crest-derived glial cells become closely associated with lateral line axons and migrate along the horizontal myoseptum as the nerve develops. In addition, since the lateral line nerve forms near the surface of the embryo, it is an ideal subject for live microscopic observation, a feature that Gilmour et al. fully exploit.

In their experimental work, the authors use an impressive array of techniques: GFP transgenics, mutants, tissue transplantation, laser ablation, and time-lapse movies of axon growth and glial migration, which graphically demonstrate the axon-glial interactions (http://www.neuron.org/cgi/content/full/34/4/577/DC1). The first question they ask is whether glia will follow the track of misdirected axons. In wild-type embryos, the dorsal and ventral muscle blocks express the growth-cone collapsing molecule *semaphorin 3A* (*sema3A*), leaving a gap at the horizontal myoseptum free of *sema3A*. Mutations such as *sonic you* (*syu*), which disrupts sonic hedgehog expression, lead both to a failure to specify the horizontal myoseptum and to ectopic expression of *sema3A*, preventing axonal growth along the normal track (Shoji et al., 1998). In *syu* or *fused-somites* (*fss*) mutants, Gilmour et al. find that axons take a circuitous route around somites, and the glia follow wherever the axons lead (see Figure). Conversely, using a laser to kill extending lateral line axons, the authors are able to stop the migrating glial precursors in their tracks. Hence, the glia migrate along lateral line axons and are unable to migrate independently of axons. The authors then asked whether axon growth was dependent on the presence of glia. In *colorless/sox10* (*cls*) mutants, glia are not properly specified and never appear at the horizontal myosepta. Mutant axons, however, extend along the correct pathway and form lateral line nerves.




Migrating Glia Follow Wherever Lateral-Line Axons Lead

(A) In wild-type embryos, *sema3A* (in blue) is expressed in dorsal and ventral somite blocks, leaving a *sema3A*-free zone at the horizontal myoseptum. Lateral-line axons (in red) grow along the horizontal myoseptum and the glia (in green) follow.
(B) In mutants, *sema3A* is expressed throughout the somites, including the horizontal myoseptum, axons are misrouted and the glia migrate where the axons lead.
(C) In *fss* mutant embryos axons are misrouted and glia (green) follow along the track laid by the axons.

The glial progenitors appear not to be needed for lateral line axon guidance, but do they have any developmental role at all? In their analysis of *cls* mutants, Gilmour and colleagues noticed that lateral line axons appeared to be somewhat frayed. They reasoned that the glial progenitors would be important for formation or maintenance of axon fascicles. To test this notion, they transplanted wild-type *zFoxD3*-GFP transgenic cells into *cls* mutant blastula. When they examined the lateral line nerves of resulting chimeric embryos, they found both bare and glial-associated regions. Bare regions of lateral-line nerve were often frayed whereas glial-associated regions were normally fasciculated.

The complexities of higher vertebrate systems have held back a detailed characterization of many important glial-axonal interactions controlling axon path-finding at the single cell level. Now, with the existing zebrafish axon guidance mutants, the zebrafish genome sequence, the ability to knock down zebrafish gene products using anti-sense morpholino oligonucleotides and the ever-growing array of transgenic zebrafish, details of the construction of the vertebrate nervous system should soon come flooding forth.

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